

Environmental Health Gold Mine in New Jersey

Michael A. Gallo, director of the NIEHS Center for Environmental Health Sciences (EHS) at the University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School on the campus of Rutgers University in Piscataway, New Jersey, offers a ready rationale for both the location and the need for the center: "New Jersey has the greatest population density in the United States—1,042 people per square mile, based on the 1990 census. We have the most Superfund sites [more than 100]. We have 3,000 other hazardous waste sites. We have an immense chemical industry, and we have a very high incidence of environmentally related diseases. New Jersey is number one in the country in breast cancer mortality."

Since its creation a decade ago, the New Jersey-based EHS center has emerged as a potent force in environmental health research. Scientists at this center made the surprising discovery that dioxins, which are liver carcinogens in animals, are also powerful inhibitors of breast cancer. Chromium contamination studies in Jersey City have helped shape federal and state clean-up and risk policies for the metal. And the detection of lead in the printing on plastic bread wrappers, which some people turn inside out and use as sandwich bags, prompted the industry to quickly get the lead out.

The center received its first funding in 1987. Since then, under first Bernard D. Goldstein and now Gallo (since 1994), it has served as an integral element of the Environmental and Occupational Health Sciences Institute. "The [EHS] center is the scientific engine that drives the institute," Gallo says. "The institute is bigger, it has a very broad mandate in the areas of worker education [and] worker training, and it does international programs. But all of the science of the institute comes from center members."

The Anatomy of the Center

The center staff numbers 75, of which 51 are scientists, all with faculty appointments at either Rutgers or the Robert Wood Johnson Medical School. Center researchers share an annual budget of nearly \$25 million, including almost \$20 million in basic and applied research grants. Three key elements make up

the center's organizational structure: four research cores, each focused on a specific scientific theme; eight facility cores, which provide auxiliary laboratory services to all center scientists; and a community outreach and education program.

The center's research cores represent its crown jewels, running studies on bio-transformation and toxicity of environmental chemicals, environmental effects on signal transduction, neural and developmental toxicology, and exposure analysis and health effects. "The mission of our center is to understand, detect, and solve environmental health problems.

Our focus is on detection and prevention, and to do that, we have the four cores," Gallo explains.

The facility cores provide vital services too expensive for a single research group to maintain. The seven established facility cores provide analytical cytometry and image analysis, chemical analysis, enzymes and antibodies analysis, exposure and dosimetry modeling, molecular genetics analysis, molecular pathology analysis, and statistical analysis.

An eighth, partially operational facility, the clinical studies laboratory, will provide center researchers opportunities to carry out human studies, such as a study on the effect of nitric oxide (NO) on signal transduction in the lungs of asthma patients. "Each of these facility cores touches every one of the research cores," Gallo says.

Gallo speaks with pride of the center's outreach effort, directed by Audrey R. Gotsch, and especially of the grade K-12 environmental education program developed for New Jersey schools. "We actually teach some of the concepts of dose and response to little kids," Gallo says. "We take it all the way up through high school, where they learn some of the fundamentals of risk assessment." The program is now used elsewhere, including classrooms in Washington State, Arizona, and Iowa. In addition to this program, Robert Snyder and Mark Robson are heading the EHS center's Rural Coalition grant in Epps, Alabama, and Chihuahua, Mexico.

The Four Research Cores

Core I. Research projects within each core are quite diverse, while adhering to each group's central theme. For example, Chung S. Yang, the center's deputy direc-

tor and co-director of Core I, along with his colleagues, including Allan H. Conney, is exploring the process by which tea may inhibit lung and esophageal cancer.

This effort began after Yang joined the center in 1989. Previous studies had yielded conflicting results. "Some of the early literature suggests tea can cause cancer," Yang says. Studies by Yang and Conney, however, found that both green and black tea can prevent these malignancies in mice and rats. No single component in tea appears preventive, Yang says. "Rather, it's a mixture of several compounds that's effective. We call them tea polyphenols."

Laboratory studies show that the tea polyphenols both retard cell proliferation, probably by inhibiting signal transduction pathways, and enhance apoptosis, the body's natural way of killing off unwanted cells. While the New Jersey researchers probe these mechanisms further, they are also trying to confirm, by various means, that tea confers benefits on humans as well as on rodents.

Bioavailability studies include measuring the polyphenol concentrations in plasma and urine, and detailed pharmacokinetic investigations in animals and humans to learn how the tea chemicals are absorbed, distributed, and cleared. Human tissues used in these studies come from surgery patients who had been given specific amounts of tea prior to their operations.

Finally, Yang is starting a human study in China's Henan Province, in an area with a high incidence of esophageal cancer. His aim is to test tea against a precancerous condition, hyperproliferation of the epithelial cells lining the esophagus. "We are trying to determine whether the tea would suppress the hyperproliferation," Yang says.

Core II. NO is a topic of great interest to scientists in Core II. The journal *Science* named NO "Molecule of the Year" several years ago in recognition of the emerging evidence of its importance in the body, including its functions as a neurotransmitter and in regulating blood pressure. Core II director Jeffrey D. Laskin, working with Diane E. Heck and Debra L. Laskin, is investigating the less beneficial aspects of NO, including its role in lung damage caused by ozone inhalation. "Ozone is a ubiquitous urban air pollutant," he explains. "Whenever there is an increase in ozone in the air, which occurs on hot summer days, there's usually a corresponding increase in hospital admissions for respiratory distress. We're trying to understand what the biochemistry is if you inhale ozone."

While the body both produces and needs NO all the time, the compound is a



free radical, a highly reactive molecule. In excessive amounts, like those generated by a heavy dose of inhaled ozone, says Laskin, "You get untoward reactions of this free radical with things it is not suppose to react with—membranes, DNA, and metal-containing enzymes—and that can cause toxicity."

Working with human cells and lab animals, the team has identified a series of biochemical events triggered by ozone entering the lung, ending in an increased production of NO. The researchers have traced most of this pathway in a series of experiments. What remains unknown is the initial event by which ozone sets this cascade in motion. "We are trying to figure out what turns it on," Laskin says. "Perhaps we could come up with some discovery that might reverse the course of toxicity."

Core III. Kenneth R. Reuhl, Core III director, also wants to find a way of reversing toxicity—in his case, the biological changes caused in the brain by low levels of heavy metals. This damage, so subtle that it often remains pathologically undetectable, results in cognitive, psychomotor, and/or motor problems. With graduate student Markus Dey, Reuhl has recently sorted out how trimethyltin and methylmercury adversely alter a key molecule in the synapses of neurons.

Neural-cell adhesion molecule 180 (N-CAM-180) is one of many cell adhesion molecules, a large family of proteins that allow cells to find and link with complementary cells and avoid connecting with inappropriate cells. Reuhl's laboratory has now shown in rodents that N-CAM-180 virtually disappears after young animals are exposed to trimethyltin for 8–12 hours. "This correlated very well with behavioral abnormalities," he says. "The trimethyltin continued to suppress the expression of N-CAM-180 for a couple of weeks. If N-CAM-180 disappeared, the animals started showing behavioral abnormalities; their ability to learn started to reappear as the N-CAM-180 started to reappear."

Methylmercury, on the other hand, affects polysialic acid residues on N-CAM-180. During cell development, these residues allow cells to migrate past one another without sticking together, Reuhl explains. The heavy metal appears to enhance and prolong the life span of the polysialic acid residues, thus inhibiting the neurons from forming synapses at the appropriate time.

Given these findings, Reuhl is trying to determine exactly how the two heavy metals modulate N-CAM-180, over what time period, and particularly if he can find a

way to reverse the ill effects of methylmercury and trimethyltin. "There is preliminary data from other labs that drugs known as cognition enhancers—which are given, for example, to patients in the early stages of Alzheimer's disease—appear to have effects on N-CAM-180," Reuhl says, "so there is some tantalizing evidence that there may be a way of intervening."

Core IV. One doesn't often find environmental health scientists involved in randomized trials. That makes the participation of Core IV researchers in several field trials unusual, to say the least.

Lead contamination in a home, largely from lead-based paint, can adversely affect the cognitive abilities of children living there. The U.S. Centers for Disease Control and Prevention has set the acceptable blood level of lead at below 10 micrograms per deciliter ($\mu\text{g}/\text{dl}$). Removing all the sources of lead in older homes is expensive and often difficult to achieve. So in the early 1990s, Core IV co-director George Rhoads and his colleagues set out to test a relatively simple strategy for lowering lead in children.

They recruited 100 Jersey City families whose children had blood lead levels of 10–20 $\mu\text{g}/\text{dl}$ for the Children's Lead Assessment and Reduction Study (CLEARS). Half the families got detailed instructions in cleaning their homes to lower lead levels and a cleaning crew visited these homes every 2 weeks for 1 year to vacuum thoroughly, dust, and wash down the walls with detergent and water. The control families received instructions in home safety and accident prevention, including general information on the dangers of lead contamination.

"At the end of the year, the children in the cleaning group had lowered their lead values by a little more than 15%, and for the children of moms who had really cooperated with us, the leads had gone down about 30%," Rhoads says. The importance, he adds, is that no specific recommendations now exist for how to deal with people who have blood lead levels in the



Center Director Michael A. Gallo

10–20 $\mu\text{g}/\text{dl}$ range. "It's clear you can make some fairly specific recommendations to a family and you can actually affect a child's blood lead, which up to this time really had not been clear," Rhoads says.

Currently, the New Jersey researchers are participating in Treatment of Lead in Children (TLC), a four-center study sponsored by the NIEHS that is designed to answer whether the chelating drug succimer will improve cognition and behavior in children with blood lead levels of 20–44 $\mu\text{g}/\text{dl}$.

Gallo relishes the opportunities New Jersey presents the center's scientists to apply a comprehensive approach to environmental health problems. "It is really exciting, in the sense that we have the capability to really go from molecule, to the whole animal, to the human," he says. "We can go from soil or air, to human, to animal, to cell, to molecule. And we can translate all that to our outreach and education program."

Patrick Young